Effect of Dose, Timing and Delivery of Tumor Necrosis Factor Alpha as an Adjuvant in Cryosurgery of ELT-3 Uterine Leiomyoma (Fibroid) Tumor

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Uterine leiomyoma (fibroid or myoma) is the most common indication for hysterectomy in premenopausal women. Cryosurgery is a uterus sparing procedure in which a myoma is frozen by a cryoprobe, thereby causing tissue necrosis upon thawing and eventual reduction in myoma size. Unfortunately, although the iceball is readily visualized (by ultrasound-US or magnetic resonance-MR), the tissue at the periphery of the iceball is not completely destroyed. One potential solution to this problem is the use of cryosurgical adjuvants that increase cryosurgical image guidance and efficacy. Previous work in our lab has shown that TNF-α (native or as the nanodrug, CYT-6091, Cytimmune Sciences, Inc.) can act synergistically with cryosurgery to destroy all prostate cancer within an iceball. Building on this work, the current study was designed to test TNF-α as an adjuvant in an in vivo model of uterine fibroid (ELT-3) in a nude mouse. The aims of this study are to characterize in vivo: 1) the destruction of the uterine fibroid over time after cryosurgery; 2) the effect of TNF-α pre-treatment on enhancement of cryosurgery; 3) the effect of TNF-α dose, pre-treatment time and mode of delivery on the above and to note any toxicities. ELT-3 rat uterine fibroid cells were grown in the hind limb of female nude mice. TNF-α at various dose (2µg and 5µg) was administered at 1, 2 and 4 hours before cryotreatment in native or CYT-6091. Native TNF-α was injected either intra-tumorally or peri-tumorally. Injecting TNF-α solution into the center of the tumor comprised the intra-tumoral approach. For peri-tumoral injection, TNF-α solution was injected at each one of eight evenly distributed points spanning the circumference of the tumor base. CYT-6091 was administered by i.v. injection only. Cryosurgery was performed with a modified 1 mm diameter cryoprobe tip (−120 °C). Freezing was allowed to continue to the visible edge of the tumor. Injury was assessed by measuring tumor-growth delay. Baseline tumor size was measured on day 0; fold-changes in tumor size are reported relative to size at day 0. Toxicity was evaluated by survival rate. Groups were 4–6 animals in each group. The data suggests that pre-treatment with TNF-α before cryosurgery significantly enhances visually guided destruction of uterine leiomyoma, and that the dose, timing and mode of delivery are important variables in optimization of this combination treatment. First, it was observed that at least four hours pre-treatment with TNF-α is required to obtain the synergistic effect of TNF-α and cryoinjury. Second, peri-tumoral injection of native TNF-α, was the most effective delivery method to enhance cryoinjury at low dose (2µg), however it was also the most toxic method at high dose (5µg). On the other hand, CYT-6091, although less effective than peri-tumoral injection at 2µg, was the safest delivery mode (0% lethality at 2µg; 33% at 5µg). Finally, CYT-6091 delivery at 5µg with cryosurgery resulted in a dramatic tumor growth delay compared with cryosurgery alone. Therefore, i.v. injection of CYT-6091 followed by cryosurgery allowed the highest dose of TNF-α, the least toxicity and the best overall myoma reduction. Funding: R01 CA075284, American Medical Systems, Inc. TNF-α and CYT-6091: Cytimmune Sciences, Inc.

Novel Transaortic Double Barrel Ventricular Cannula

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A novel transaortic ventricular cannula, known as the 'double barrel' cannula (DBC), is designed to minimize the invasiveness of Ventricular Assist Device (VAD) implantation by combining the inlet and outlet cannulae into a single dual lumen cannula. Both flows will pass through a single opening in the apex of the Left Ventricle with the outflow then continuing past the aortic valve, into the aortic arch. This design offers several potential advantages over the current state-of-the-art. These include less invasive surgery and providing mechanical support to the septum. By routing the outflow through the aortic valve, the need to access the external structure of the ascending aorta is eliminated thereby eliminating the need for open heart surgery. In determining the DBC’s design, close attention has been paid to the outflow portion of the cannula, which passes through the aortic valve. It was anticipated that this portion of the DBC could have the largest impact on the device’s usability in practice. The object of this study was to test the performance of the valve with the cannula passing through it. Three different geometries are circular, equilateral triangular, and one-third semicircular. Experiments measuring aortic insufficiency during the diastolic phase were conducted. The experiment was designed to analyze several geometries passing through an aortic valve under diastolic flow conditions. All experiments used a simple flow loop which allows a natural porcine aortic valve to be viewed from downstream. The loop was driven with a pneumatic ventricular simulator in order to produce a cyclic flow. Three cannulae cross-sections were molded from RTV11 Silicone. During this test, High Speed Cinematography and flow rate measurement were used to quantify valve sealing and leakage. All data was collected and analyzed for the three cross-sectional geometries during diastole. The performances of the three geometries were compared using American Heart Association guidelines of aortic insufficiency (AI) diagnosis. The flow rate data was integrated in order to determine the volume of ventricle ejection and valve regurgitation. All three geometries exhibit low and acceptable levels of AI (<15% AI), with the circular geometry causing the least amount of AI at 7.1%. The experimental control (Porcine aortic valve with no cannulae) exhibited an AI or 2.4%, validating both the harvested aortic valve and experimental flow loop for further testing. Using the high speed cinematography, several phenomena were observed during the sealing of the porcine valve; including leaflet folding leaflet bunching, and cannula displacement due to valve closure.